Cardiorenal Syndrome

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Definition and Classification of the CRSs

- Acute Dialysis Quality Initiative (ADQI) group proposed a definition and classification of CRS and discussed management strategies (Ronco C, etal Eur Heart J, 2010).
- CRS is defined as : “Disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other”
- They suggested that the syndrome be classified into five distinct types depending on whether heart or kidney was the initial organ of insult .

- In types 1 and 2 CRS, worsening of HF in acute (type 1) or chronic HF (type 2) leads to worsening kidney function. In types 3 and 4 (termed acute and chronic renocardiac syndromes, respectively), AKI or CKD leads to worsening HF. In type 5 CRS, systemic conditions cause simultaneous dysfunction of the heart and kidney.

- It should be mentioned that the temporal sequence of organ dysfunction largely distinguishes type 1 (cardiac first) from type 3 (renal first). However, it is not only the timing, but also the predominance of the problem that allows the correct determination.

Table 1. Definition of different types of CRS

CRS type 1	Acute worsening of heart function causing acute kidney injury and/or dysfunction
CRS type 2	Chronic abnormalities in cardiac function leading to progressive CKD
CRS type 3	Sudden worsening of renal function causing acute cardiac injury and/or dysfunction
CRS type 4	Condition of primary CKD leading to a reduction in cardiac function (ventricular hypertrophy, diastolic dysfunction) and/or increased risk of cardiovascular events
CRS type 5	Systemic disorders (e.g. sepsis) that concurrently induce cardiac and kidney injury and/or dysfunction

Prevalence and Incidence of Types 1 and 2 CRS

- In the Acute Decompensated Heart Failure National Registry (ADHERE), over 60% of patients admitted to US hospitals with acute decompensated HF (ADHF) had stage 3 (GFR,60 ml/min per 1.73 m2) or worse CKD (Heywood JT, etal, J Card Fail , 2007).
- The prevalence of CKD (type 2 CRS) is seen in 32%–50% of patients in the large chronic HF trials (Anand IS, etal,Circulation, 2009).
- According to recent data, patients with evidence of CKD have a 10- to 20-fold increased risk for cardiac death compared to age- and sex-matched controls (Ronco C, etal Blood Purif 2009).

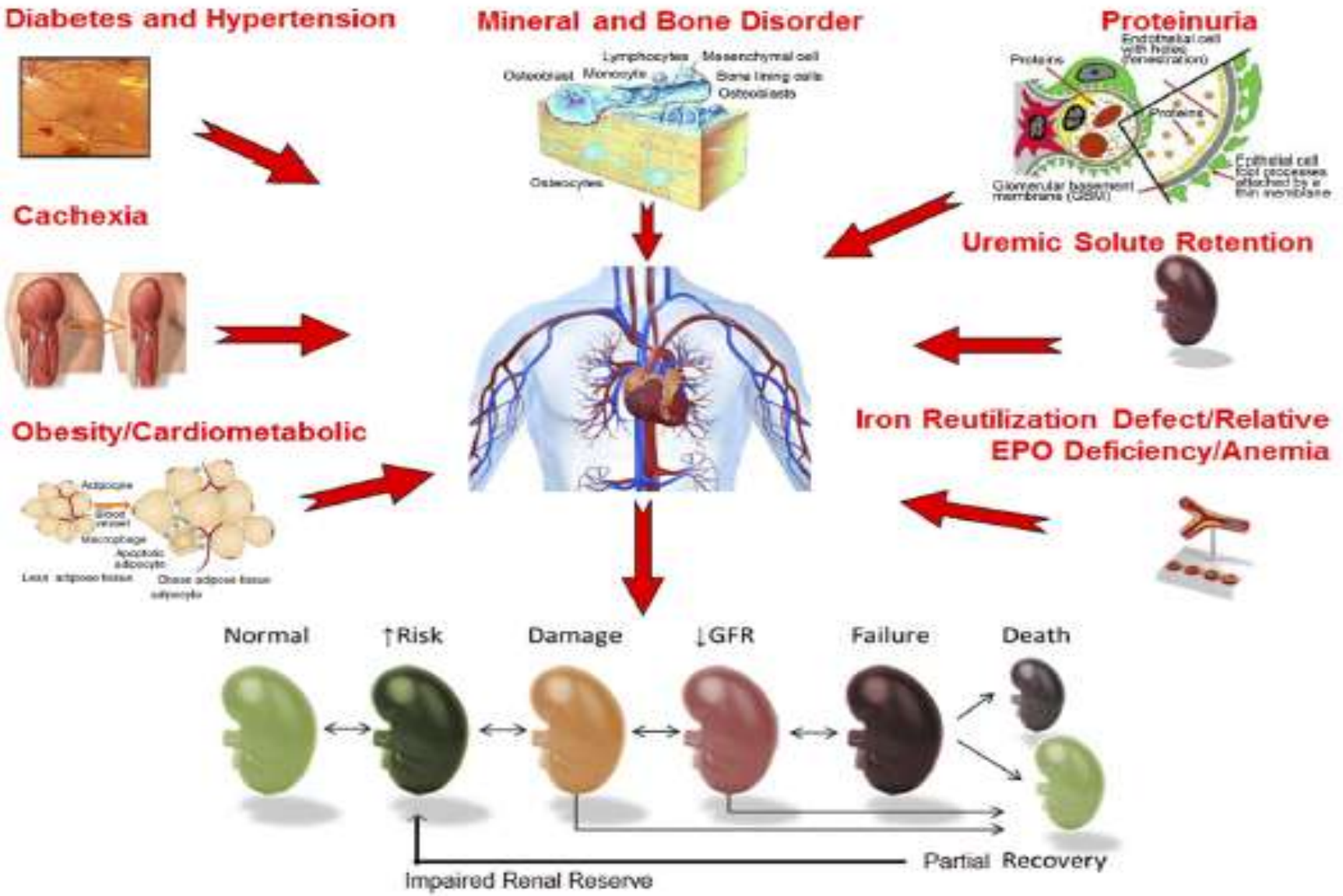


Figure 2 Predisposing Factors for CRS

Obesity and cardiometabolic changes in the cardiovascular system, including diabetes and hypertension, and later in the course of disease, cachexia, biochemical, and hormonal changes due to bone and mineral disorder, proteinuria, uremic solute retention, and anemia, all contribute to the risk for developing cardiorenal syndrome (CRS) type 1. The course of this syndrome can lead to permanent renal failure and need for dialysis or partial renal recovery. EPO = erythropoietin; GFR = glomerular filtration rate.

Obesity:

- The adipocytes secrete cytokines, and as a result, these cytokines may cause cardiac and renal injury, as for example interleukin IL-6 and tumor necrosis-factor alpha, which are both secreted by adipocytes have been implicated in both heart and kidney disease.
- The production of IL-6 by abdominal adipocytes into the portal circulation and transit to the liver is the most important stimulus for release of high-sensitivity C-reactive protein. Thus, high-sensitivity C-reactive protein levels are highest in obese individuals and fall to a greater extent with weight loss than any other intervention ,(Ouwens DM, etal , J Cell Mol Med 2010).

Cachexia :

- combined disorders of the heart and kidney are likely to develop in the presence of some degree of cachexia and sarcopenia and are associated with organ crosstalk via tumor necrosis factor-alpha and other pro-inflammatory cytokines (Cicoira M, etalCytokine,2010).
- In these circumstances, a vicious circle could arise, in which cachexia and nutritional deficiencies associated with either HF or CKD may contribute to further damage and fibrosis of the other organ (McCullough PA. etal,Blood Purif 2011).

Uremic solute retention :

- Studies have demonstrated that uremia causes myocyte dysfunction manifested by impaired movement of calcium in the cytosol leading to impaired contraction of myocyte elements (Periyasamy SM, Chen J, Cooney D, et al. Kidney Int 2001).
- In addition, uremia directly contributes to accelerated fibrosis and adverse cardiac remodeling after myocardial infarction (Dikow R, Schmidt U, Kihm LP, et al.Am J Nephrol,2010).
- Relief of chronic uremia with renal transplantation has been associated with many changes, including improvement in left ventricular systolic function, reduction in left ventricular mass, and reduction in left ventricular size.

Iron and oxidative oxidative Stress :

- Oxidative stress is a final common pathway for cellular dysfunction, tissue injury, and organ failure.
- The most widely recognized chemical reactions generating reactive oxygen species are the Haber-Weiss and Fenton equations.
- These equations require oxygen, water, hydrogen, and a metal catalyst in the form of iron, copper, and so on.
- Since iron is the most abundant metal element in cells, it is believed that labile iron is the major stimulus for oxidative stress that results in tissue injury (Ronco C, etal Semin Nephrol 2012).

- The release of poorly liganded labile iron that remains unbound in a fraction has been implicated in both acute ischemic cardiac models and a variety of injury models in the kidney (Shah SV, etal Hemoglobin 2009).
- Importantly, labile iron transitioning from Fe2 to Fe3 facilitates the production of hydrogen peroxide and the dangerous hydroxyl radical, which overwhelm the homeostatic antioxidant defense mechanisms in cells (Whaley-Connell etal Rev Cardiovasc Med 2011).
- therapeutic attempts to substantially attenuate oxidative stress, in theory, hold promise for large benefits in patients with CRS

Hyperuricemia :

- Hyperuricemia is associated with uremia and has been associated with atherosclerosis and cardiovascular death in multiple studies (Feig DI, et al N Engl J Med 2008).
- Observational studies of patients with gout and HF have shown that allopurinol is associated with improved outcomes (Thanassoulis G, etal Arch Intern Med 2010).

Inflammation and immune cell signaling :

- Inflammatory cytokines may be produced by cardiomyocytes, following ischemic or mechanical stimuli, but also by the innate immune response, represented by Toll-like receptors, pentraxin-like C-reactive protein, and pentraxin 3 (Torre-Amione G. Am J Cardiol 2005).
- There is evidence supporting the prognostic value of various circulating markers of inflammation, particularly C-reactive protein, pentraxin 3, tumor necrosis factor-alpha, IL-1, and IL-6 (Heymans S, Hirsch E, Anker SD, et al. Eur J Heart Fail 2009)

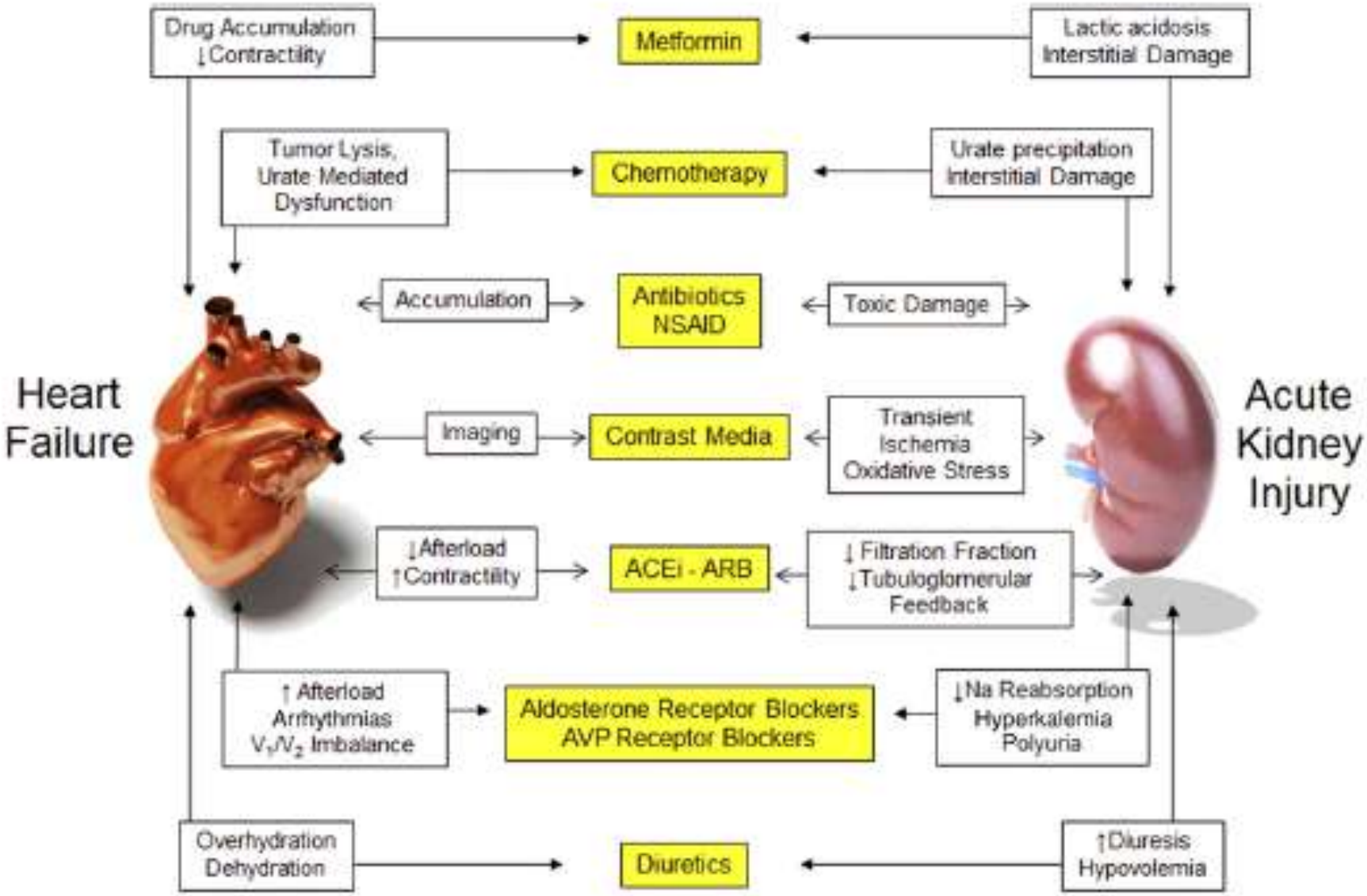


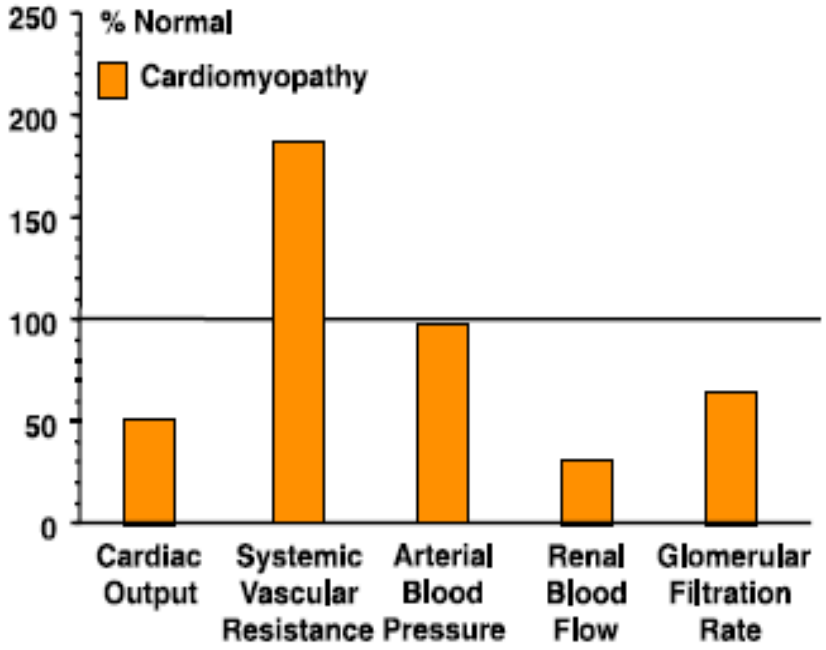
Figure 4 Iatrogenesis and Type 1 CRS

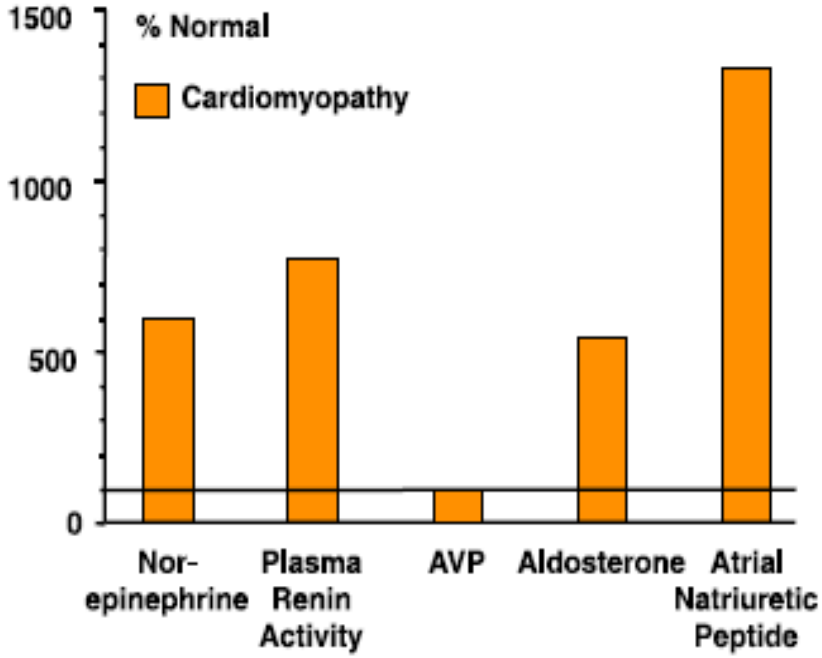
Multiple sources of iatrogenic injury, some of which may be unavoidable, can result in either cardiac, renal, or cardiorenal impairment and kidney damage in patients with acutely decompensated heart failure (ADHF). ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; AVP = arginine vasopressin; NSAID = nonsteroidal anti-inflammatory drug.

Pathogenesis of Renal Dysfunction in HF

- Several mechanisms have been implicated in the pathogenesis of renal dysfunction and worsening renal function in HF.
- The hemodynamic consequences of reduced cardiac output (CO) with low renal perfusion and activation of the sympathetic and renin-angiotensin - aldosterone system (RAAS) probably play the most prominent role in initiating renal dysfunction, salt and water retention, and venous congestion.
- Anemia, a common comorbidity in HF, can also worsen renal function.
- Drugs, such as blockers of RAAS used for the treatment of HF or nonsteroidal antiinflammatory drugs and cyclosporine used for the management of comorbidities, may contribute to worsening renal function.
- Primary renal parenchymal disease related to longstanding diabetes and hypertension, common comorbidities in HF, may also worsen renal function.

Role of Hemodynamic Abnormalities in the Pathogenesis of CRS





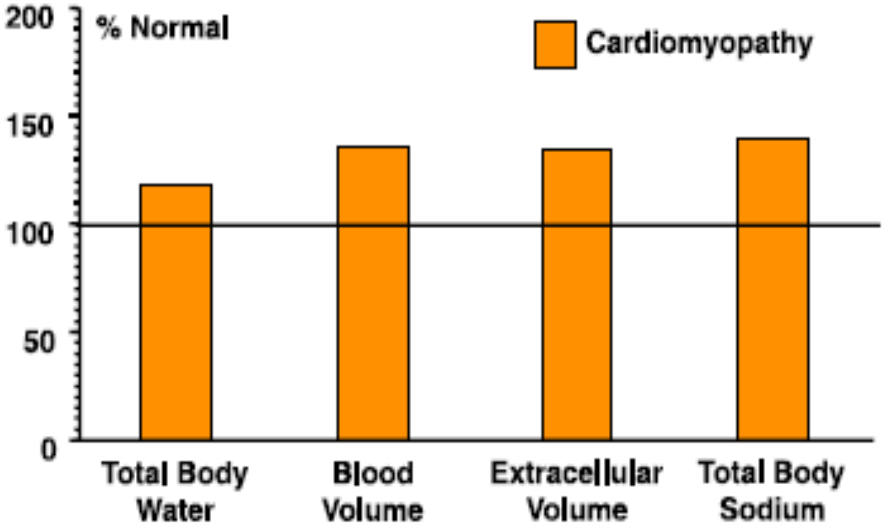


Figure 1. | Bar graphs showing hemodynamic, renal function, plasma hormones, and body fluid compartment data expressed as percent of normal in a group of patients with untreated congestive heart failure. Data are from reference 27. AVP, arginine vasopressin.

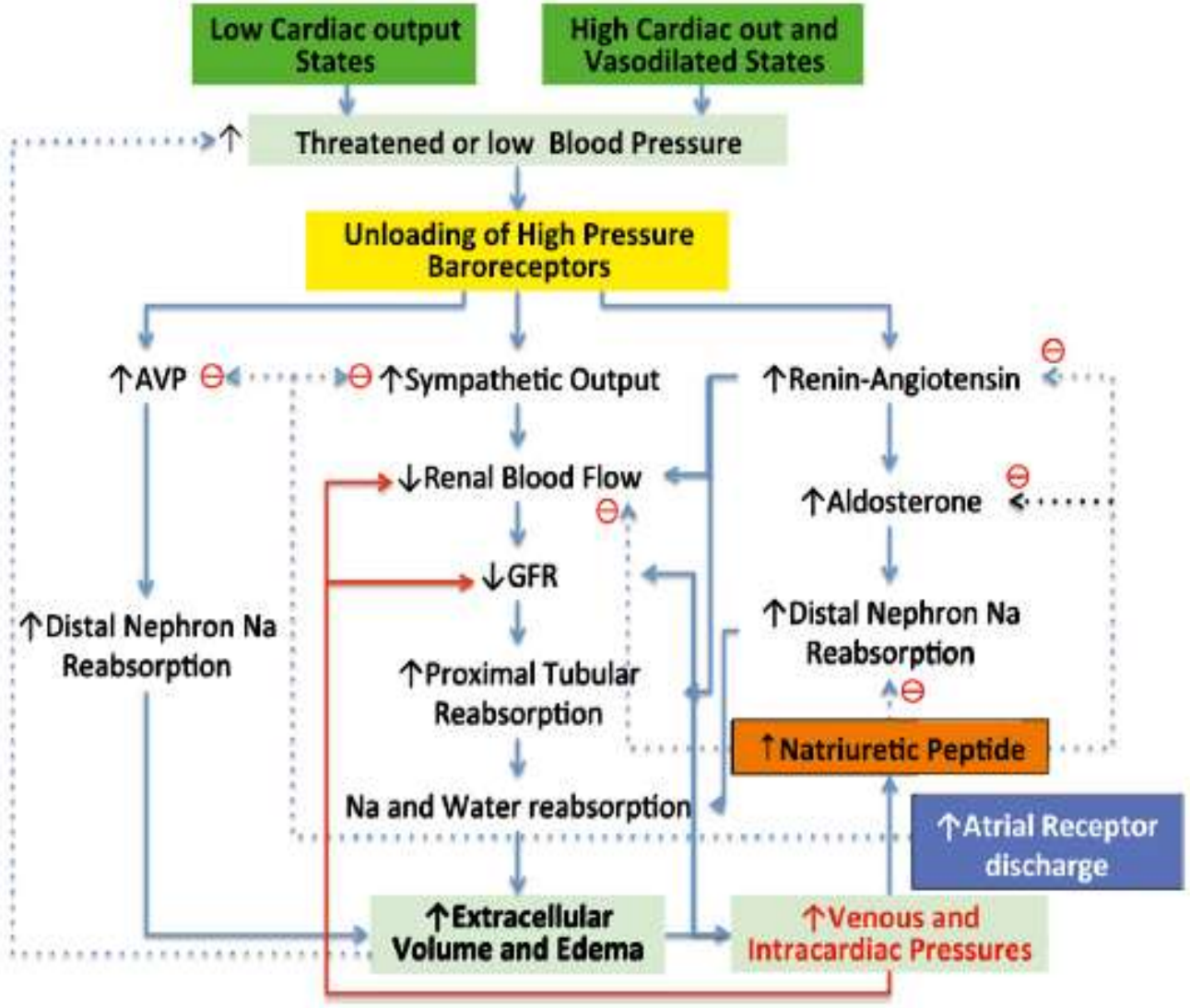
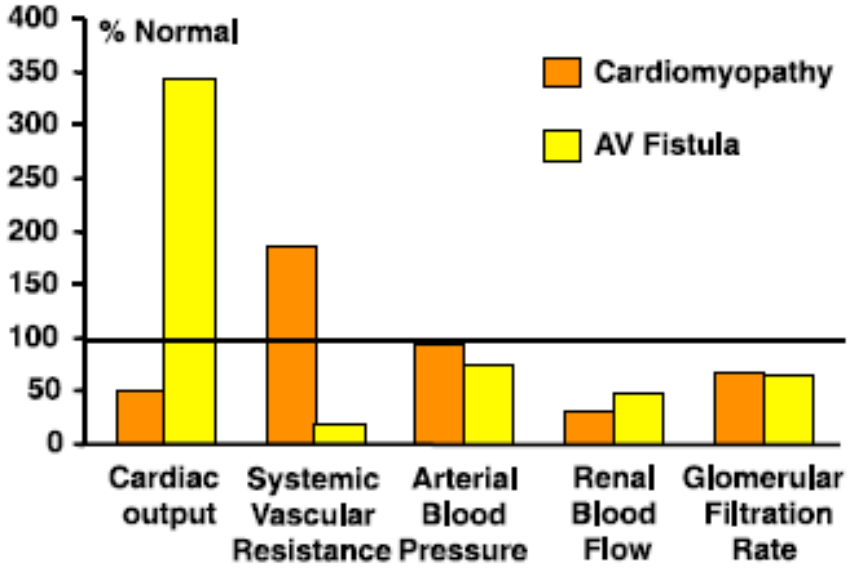
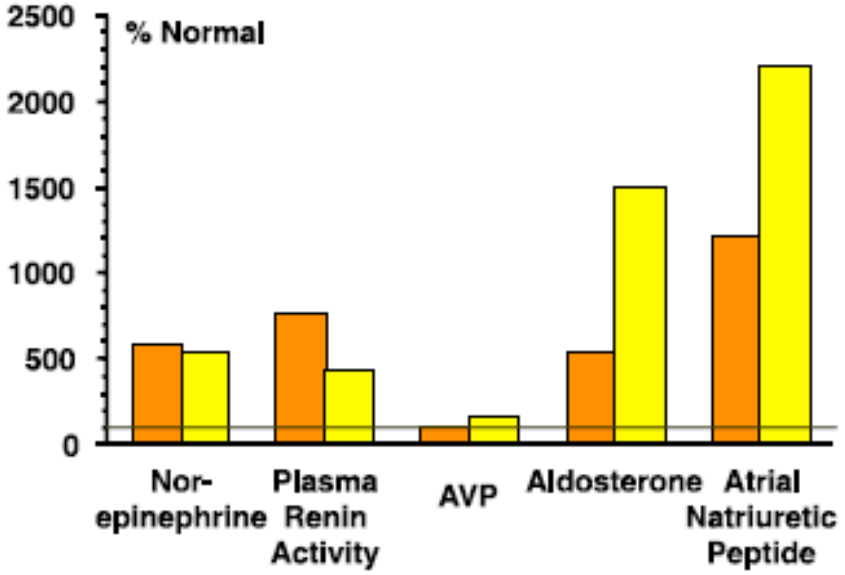


Figure 3. | Diagram showing the sequence of events that leads to salt and water retention by the kidney and development of renal dysfunction. Notice that, in both low and high cardiac output heart failure, the common stimulus seems to be a threat to the arterial BP. The direct effects of these mechanisms are shown by solid blue lines, and mechanisms that may help to improve renal function are indicated by the dotted blue lines and red symbol. The role of increased venous pressure in worsening renal function is shown in red lines. Modified from reference 32, with permission.





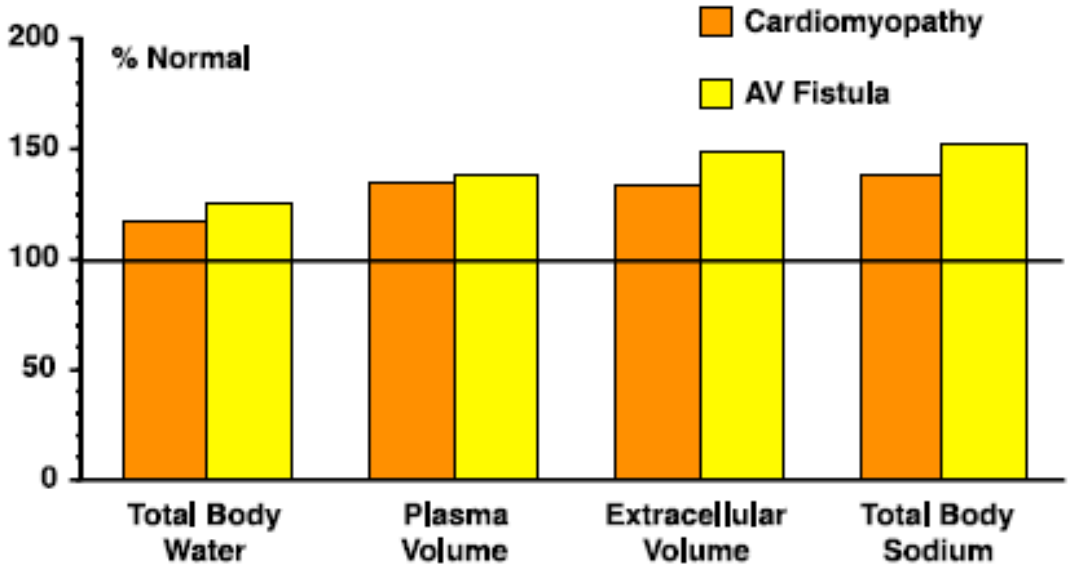


Figure 4. | Bar graphs comparing the hemodynamic, renal function, plasma hormones, and body fluid compartment data of patients with untreated low-output heart failure with data from patients with untreated high-output heart failure because of a large arteriovenous fistula. Despite dissimilar hemodynamics, the neurohormonal activation, fluid retention, and renal dysfunction were very similar in low- and high-output heart failure. Data are from references 27 and 31.

Role of High Venous Pressure in the Pathogenesis of CRS

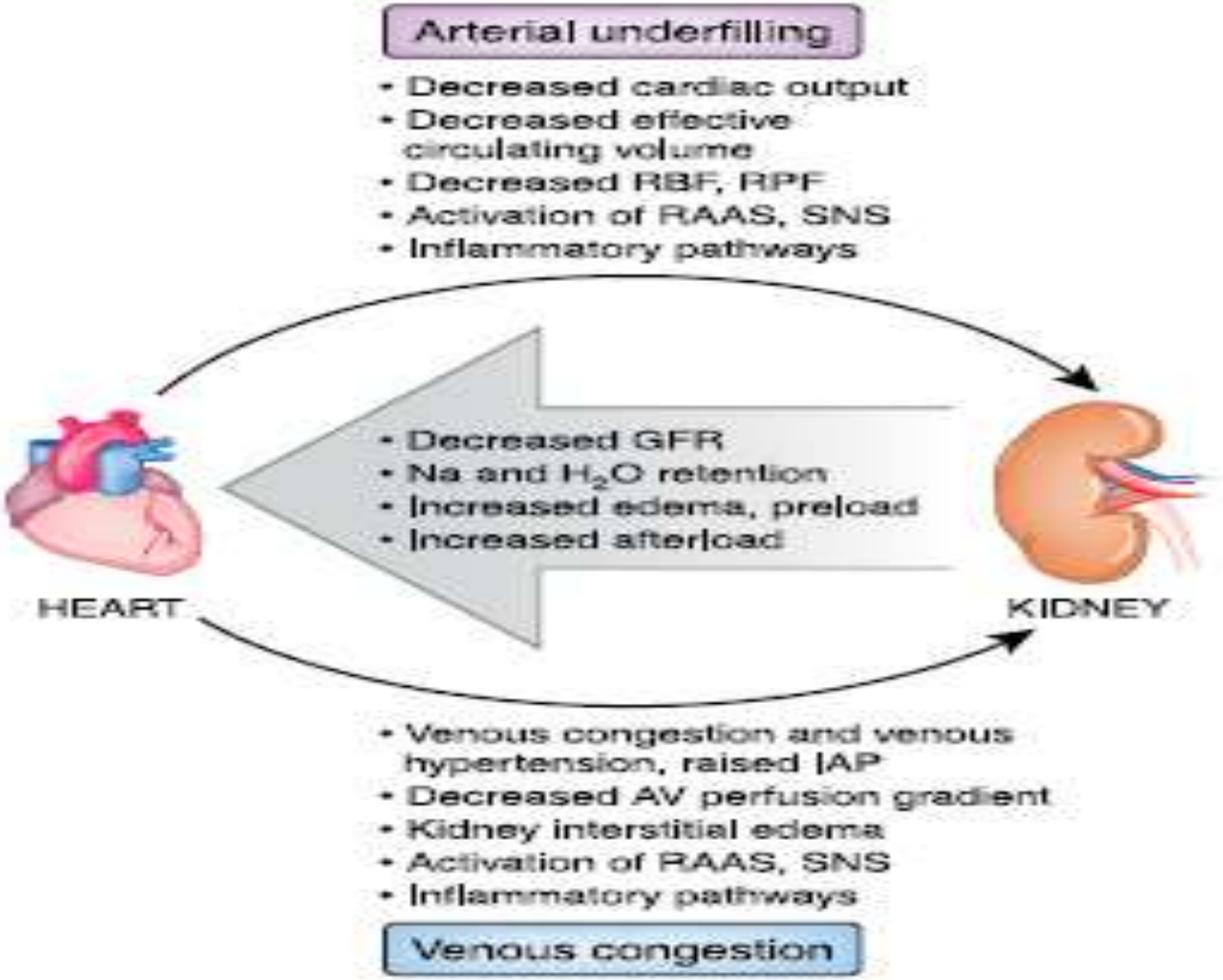
- Damman et al. (2009) found that higher CVP was inversely related to GFR and independently associated with allcause mortality. Similar findings were reported by Mullens et al. (2009) in patients admitted with ADHF, and it was found that there was an incremental risk of developing worsening renal function (serum creatinine.0.3 mg/dl) with increasing CVP independent of the CO.
- In addition to its effects on renal hemodynamics, high systemic venous congestion can activate endothelial dysfunction with production of reactive oxygen species, TNFa, endothelin-1, IL-6, and other inflammatory cytokines , all of which worsen nitric oxide dysregulation, resulting in additional neurohormonal activation and renal dysfunction.
- Venous congestion may also trigger production of systemic endotoxins from the gut, and superimposed infection may also contribute to renal dysfunction.

Why should an increase in venous pressure decrease renal function?

- An increase in renal venous pressure decreases the arteriovenous pressure gradient across the kidney and reduces the already compromised RBF, causing GFR to decrease.
- Because the kidneys have a tight capsule, an increase in venous pressure is also likely to increase renal interstitial pressure and therefore, the pressure in the renal tubules.

Is the Renal Dysfunction Reversible?

- in many patients, the renal dysfunction is reversible if the hemodynamics can be improved. in other patients, the underlying structural renal disease may contribute to permanent renal dysfunction.



Dual hemodynamic pathways for acute cardiorenal syndrome.

Cardiorenal Syndrome Type 4

- Cardiorenal syndrome type 4 (CRS type 4) is characterized by primary chronic kidney disease (CKD) leading to an impairment of cardiac function, with ventricular hypertrophy, diastolic dysfunction, and/or increased risk of adverse cardiovascular events.
- The incidence of CKD is increasing, and CRS type 4 is becoming a major public health problem associated with a high morbidity and mortality.
  Cardiorenal Med 2013

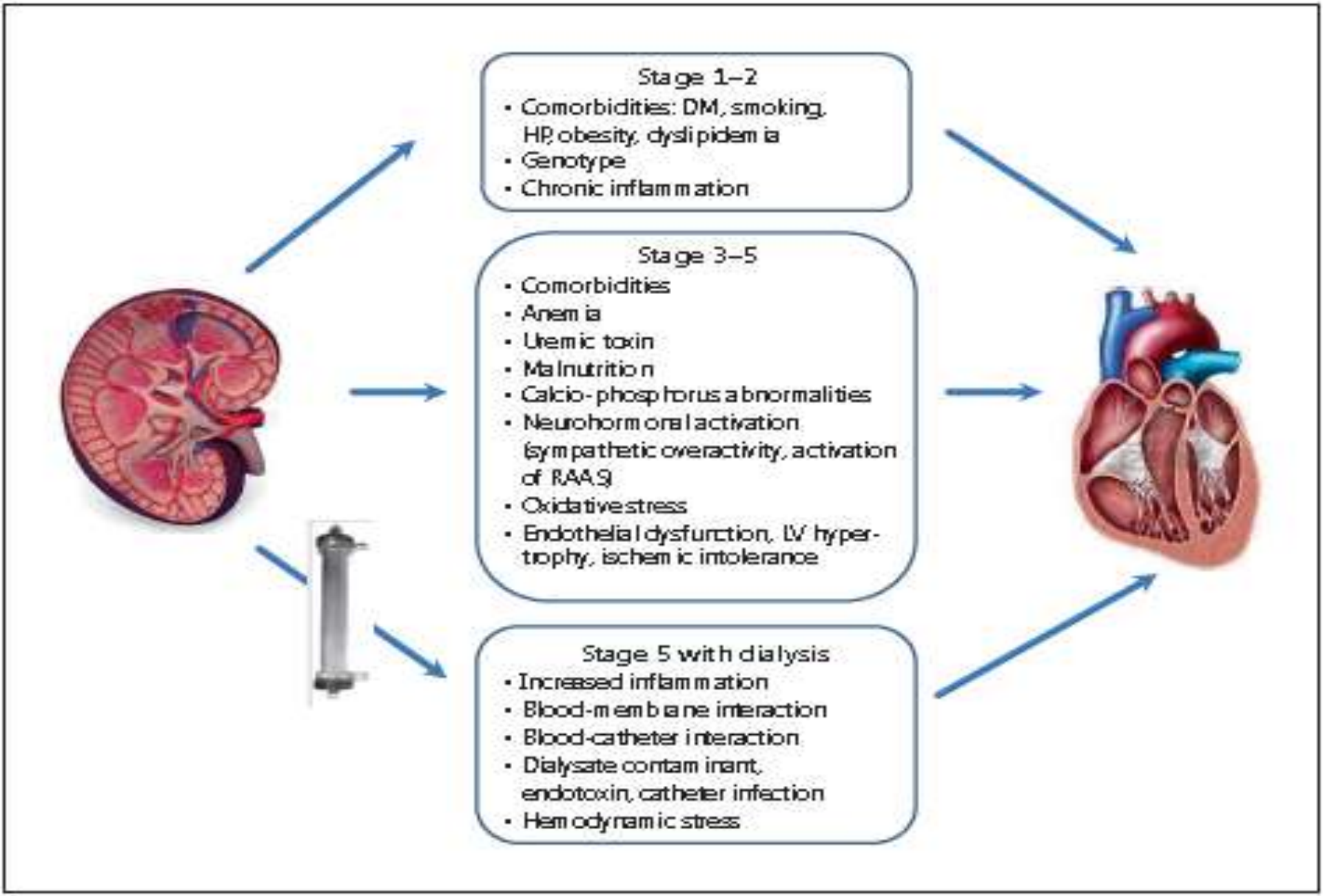


Fig. 1. Schematic of CRS type 4 (chronic renocardiac syndrome). DM = Diabetes mellitus; HP = Hypertension; RAAS = renin angiotensin aldosterone system.

Abdominal Contributions to Cardiorenal Dysfunction in Congestive Heart Failure

Frederik H. J Am Coll Cardiol 2013

- The abdominal compartment might contribute significantly to deranged cardiac as well as renal function in CHF.
- Abdominal symptoms of congestion are not uncommon in CHF, with constrictive pericarditis and restrictive cardiomyopathies being extreme examples in which splanchnic venous hypertension and the formation of ascites often occur.
- Maladaptive derangements in the abdominal compartment might affect cardiorenal efficiency in CHF.

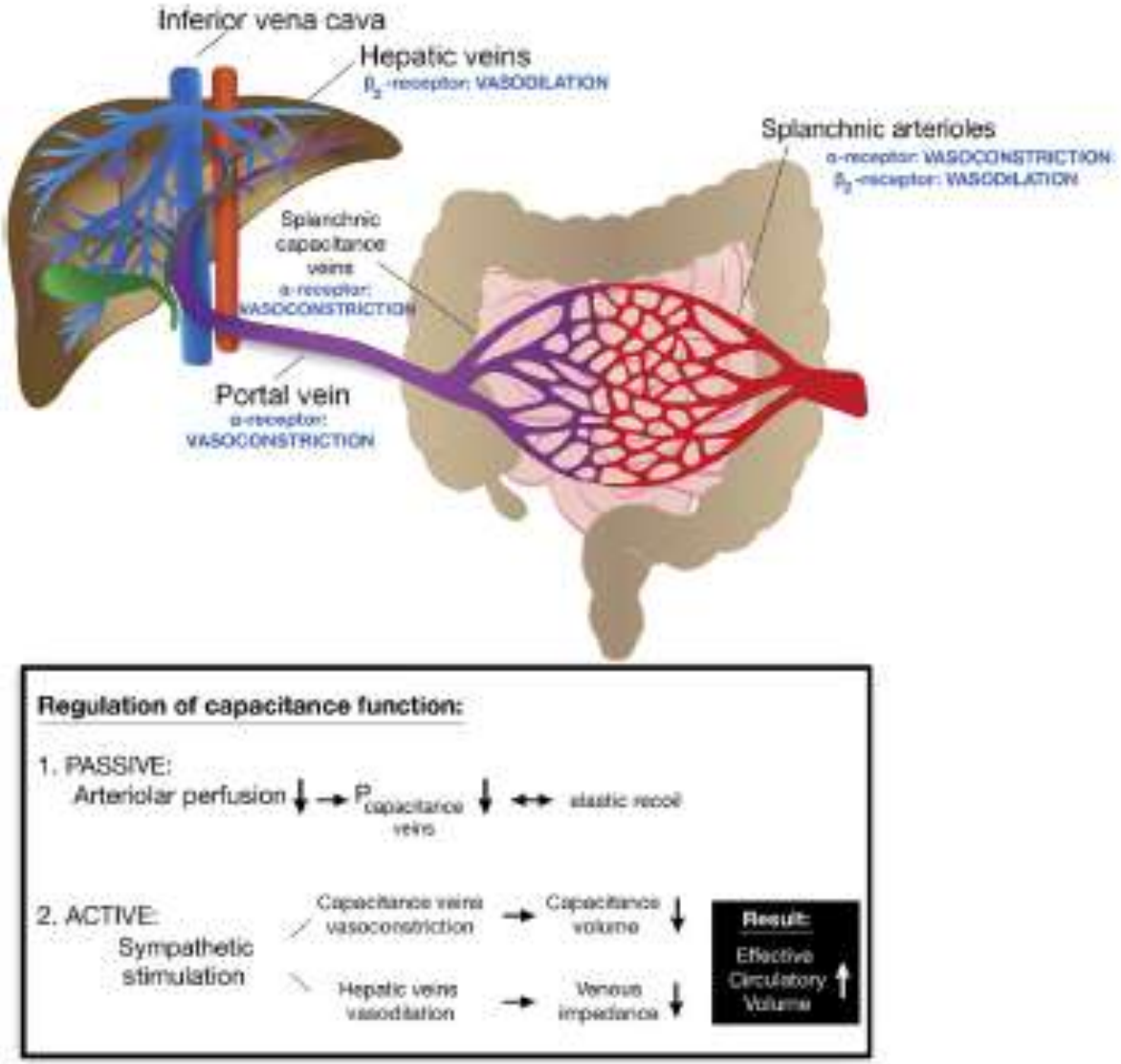


Figure 1 The Splanchnic Vasculature: Capacitance Function and Cardiac Pre-load

Splanchnic capacitance veins ensure a stable cardiac pre-load in the face of a changing volume status. First, if arteriolar perfusion drops, elastic recoil of the veins maintains a driving force for venous return. Second, sympathetic stimulation because of centrally perceived hypovolemia leads to a-mediated vasoconstriction of splanchnic capacitance veins, but b2- mediated vasodilation of the hepatic veins. Consequently, autotransfusion from the splanchnic capacitance veins occur to increase the effective circulatory volume.

The intestinal barrier function, gut microbiota, and uremic toxicity.

- Arterioles, capillaries, and venules have a peculiar organization in the intestinal microcirculation, forming a countercurrent system that strongly resembles the vasa recta of the renal medulla.
- As a result, the intestinal villus can build up an interstitial concentration gradient with the highest osmolality at its tip, which is needed for continuous fluid absorption.
- However, a drawback of this system is that arteriolar oxygen short circuits to venules before reaching the villus tip, making this place particularly susceptible to anoxic damage .
- Indeed, it has been shown that the intestinal morphology, permeability, and function are substantially altered in CHF, especially in advanced states with cardiac cachexia .
- Moreover, concomitant uremia caused by renal dysfunction alters the bacterial colonization of the gut and may also contribute to increased intestinal permeability .
- It has been demonstrated that microbiota are the cause of fermentation processes in the gut, which produce protein-bound uremic toxins that are ineffectively cleared from the circulation in cases of renal dysfunction .
- Moreover, lipopolysaccharide in the circulation triggers systemic inflammation and cytokine generation (i.e., tumor necrosis factor-a, interleukin-6), which results in depression of excitationcontraction coupling, decreased peak velocity of cardiomyocyte shortening, disturbed mitochondrial respiration, and impaired substrate metabolism in cardiomyocytes .

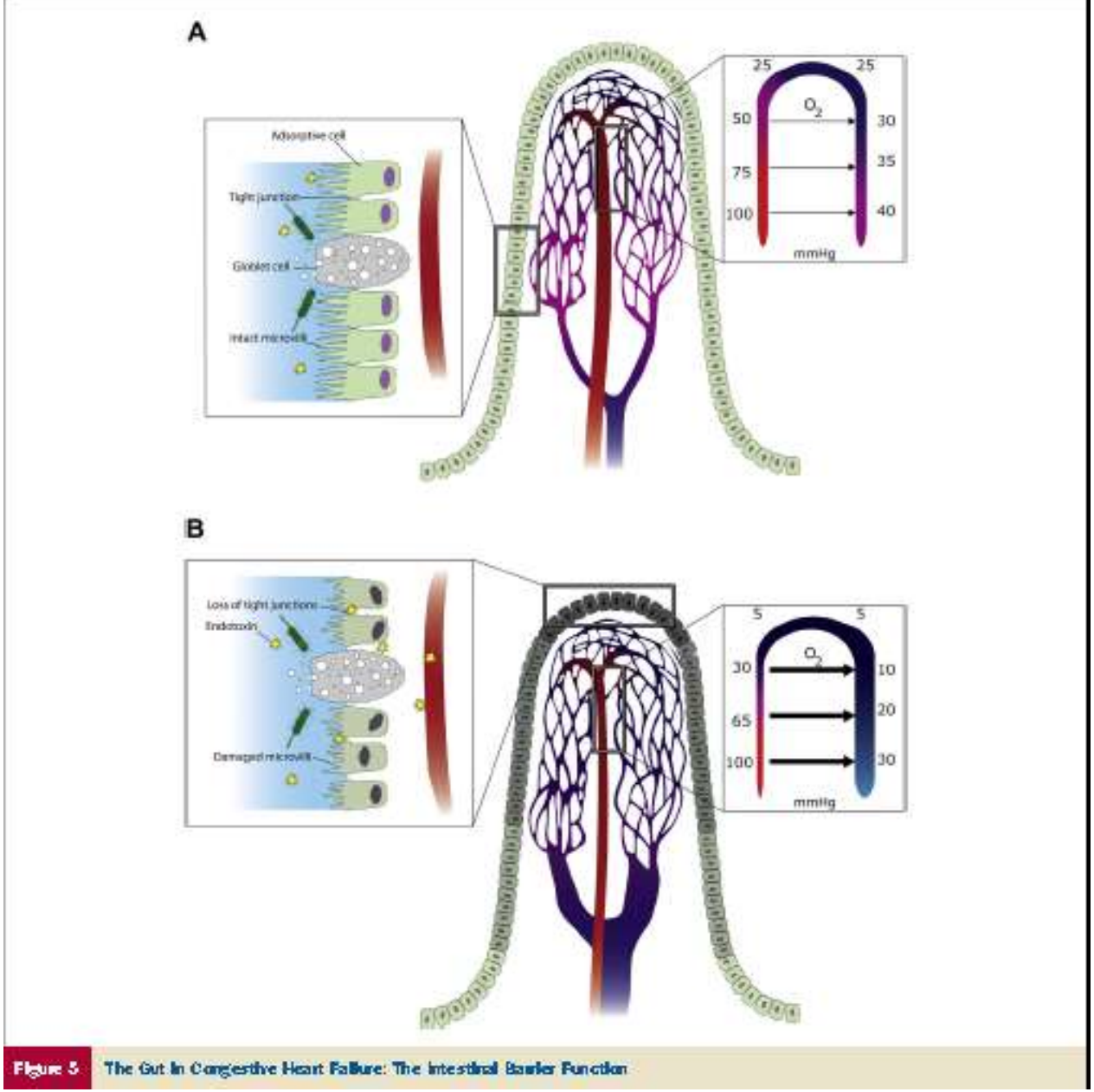
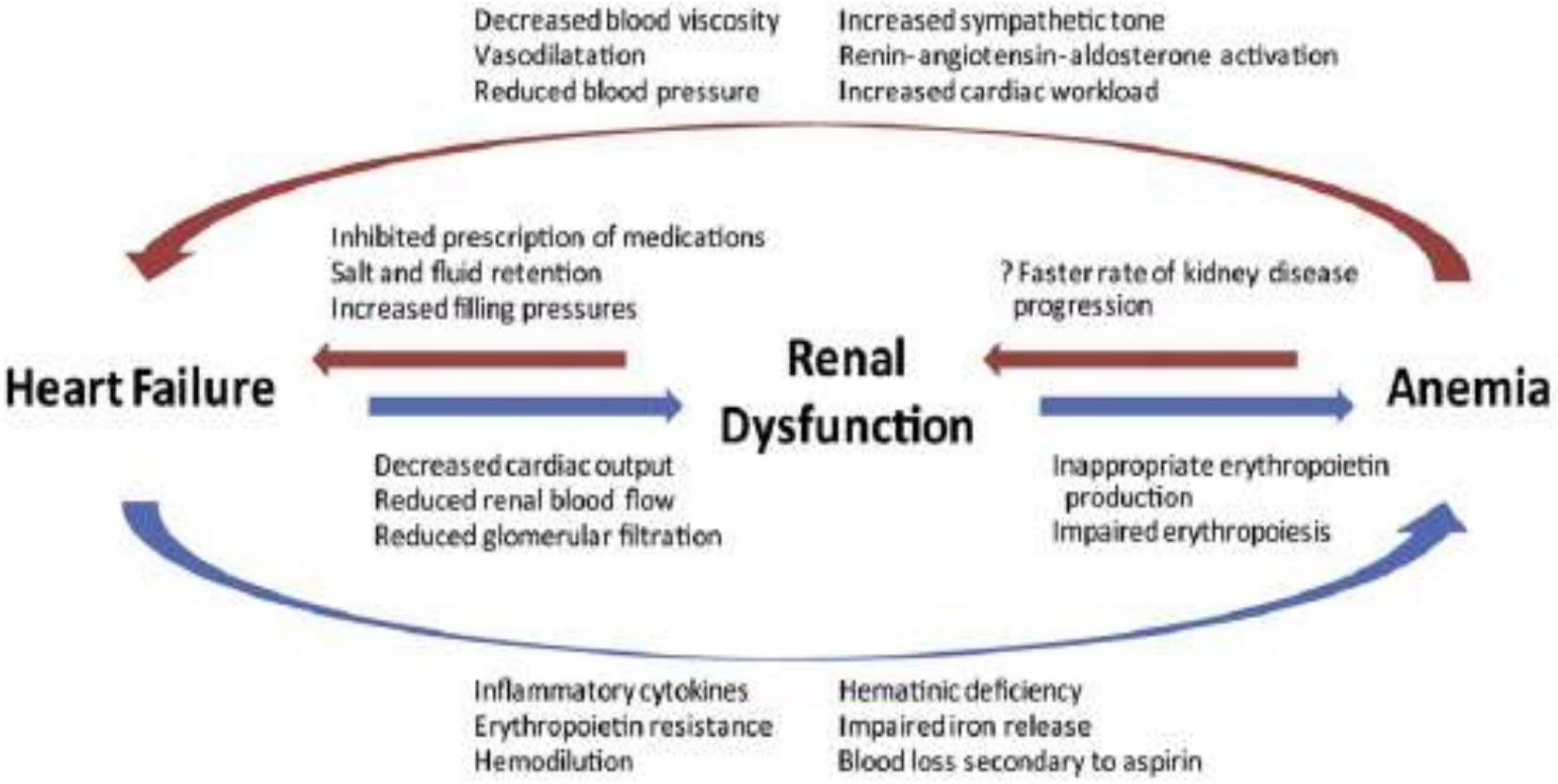


Figure 3 The Gut in Congestive Heart Failure: The Intestinal Barrier Function

(A) The countercurrent system of the intestinal microcirculation makes extensive exchange possible between arterioles and venules. As a result, oxygen (O2) short circuits from arterioles to venules, creating a gradient with the lowest partial O2 pressure at the villus tip. (B) In congestive heart failure, there is a low-flow state in the splanchnic microcirculation because of low perfusion, increased venous stasis, and sympathetically mediated arteriolar vasoconstriction, which stimulates O2 exchange between arterioles and venules, exaggerating the gradient between the villus base and tip. This causes nonocclusive ischemia, resulting in dysfunctional epithelial cells and loss of intestinal barrier function. As a result, lipopolysaccharide or endotoxin, produced by gram-negative bacteria residing in the gut lumen, enter the circulatory system.



The cardiorenal anemia syndrome. Pathophysiology of anemia in patients with heart failure.

Predictors of CRS

- In the Valsartan I Heart Failure Trial, age, men, diabetes, ischemic etiology of HF, low BPs, worse neurohormonal and proinflammatory profiles, presence of edema, and use of higher doses of diuretics were independently associated with the presence of CKD (Anand IS etal , Circulation 2009).
- Interestingly in the CHARM trial, the variation of left ventricular (LV) ejection fraction was not associated with the presence of CKD.

Biomarkers for the Early Identification of CRS Type 4

Cardiac Biomarkers:

- troponins, plasminogen activator inhibitor type I, homocysteine, brain natriuretic peptide (BNP), C-reactive protein, serum amyloid-A protein, ischemia-modified albumin, and advanced glycation end-products have been demonstrated to correlate with cardiovascular outcomes in CKD patients (Mutluay R, etal,Ren Fail 2010).

Renal Biomarkers:

- cystatin C (CysC) and neutrophil gelatinase-associated lipocalin (NGAL) have been recently found to be diagnostic and prognostic markers of cardiovascular outcomes in CKD (Iwanaga Y,etalCirc, J 2010).

- Higher levels of CysC have been demonstrated to be directly involved in the atherosclerotic process (Ix JH, etal,Circulation 2007) ;and are associated with increased LV mass and its concentricity independent of renal function (Patel PC, etal,Circ Heart Fail 2009).

- Increased NGAL expression has been found in atherosclerotic plaque and failing myocardium in patients with CAD and heart failure . Its levels correlated with disease severity independent of coexisting renal injury (Yndestad A, etal,Eur Heart J 2009).

Prognosis of CRS

- Both types 1 and 2 CRS are independently associated with increased mortality and morbidity in patients with ADHF and chronic HF (Nohria A , etal J Am Coll Cardiol,2008.).
- In the ADHERE registry , the in-hospital mortality increased from 1.9% for patients with normal renal function to 7.6% for patients with severe renal dysfunction (P,0.001) (Heywood JT, etal J Card Fail , 2007).

Management of CRS Type 4

Medical Therapies to Improve Cardiovascular Outcomes:

- CKD is associated with increased sympathetic activity and renin angiotensin aldosterone system (RAAS) activation which may induce chronic inflammation and oxidative stress.
- Pun et al. [Clin J Am Soc Nephrol 2007] found that the use of ACEIs or angiotensin receptor blockers (ARBs) and beta-blockers (BBs) was significantly associated with improved survival in ESRD patients after cardiac arrest.
- Cice et al. [J Am Coll Cardiol 2003] randomized 114 dialysis patients to receive carvedilol or placebo and demonstrated a significant reduction in cardiovascular mortality and a trend towards a reduction in the occurrence of sudden death.

Dialytic Strategies to Improve Cardiovascular Outcomes:

- Advances in dialysis technology may improve hemodynamic stability, reduce oxidative and inflammatory stress and produce more efficient removal of low and middle toxins leading to the concept of 'cardioprotective dialysis'.
- A Cochrane meta-analysis on biocompatible membranes revealed a reduction in the beta-2-microglobulin (β2M) level, an increase in albumin concentration, and an improvement of Kt/V, although mortality was not affected (Cochrane Database Syst Rev 2005:CD003234).
- House et al. [Nephrol Dial Transplant 2000] did not find any benefit of high-flux polysulfone membranes compared with low-flux membranes in terms of lipids and homocysteine levels in a controlled trial.
- In contrast, Chauveau et al. [Am J Kidney Dis 2005] , in an observational study, have shown that high-flux membranes were associated with improved 2-year survival.
- Different studies have reported that 'hemofiltration' or 'hemodiafiltration' treatment was associated with better blood pressure control, lower incidence of intradialytic hypotension or arrhythmia, better β2M and phosphate clearance, reduced inflammation and oxidative stress as well as reduced hospitalization rate (Hemodial Int 2006).
- some data suggest that PD is associated with a lower mortality than HD in the first 1–2 years; afterwards, the mortality may be higher on PD than HD.

Cardiorenal Syndrome: Ultrafiltration Therapy for Heart Failure—Trials and Tribulations

Amir Kazory Clin J Am Soc Nephrol 8: 1816–1828, 2013

- The suboptimal efficacy and safety profile of diuretic-based therapeutic regimens coupled with unsatisfactory results of the studies on novel pharmacologic agents have positioned ultrafiltration on the forefront as an appealing therapeutic option for patients with acute decompensated heart failure (ADHF)

Table 1. **Potential shortcomings of diuretic use in treatment of heart failure**

Direct activation of the renin-angiotensin-aldosterone system
Deterioration in renal function
Electrolyte abnormalities (*e.g.*, hypokalemia and hypomagnesemia)
Suboptimal natriuresis (production of hypotonic urine)
Development of diuretic resistance
Unpredictability of the therapeutic response
Lack of clarity on the practical aspects of use (*e.g.*, optimal dosing strategy)
Nonrenal adverse effects (*e.g.*, ototoxicity and hypersensitivity)

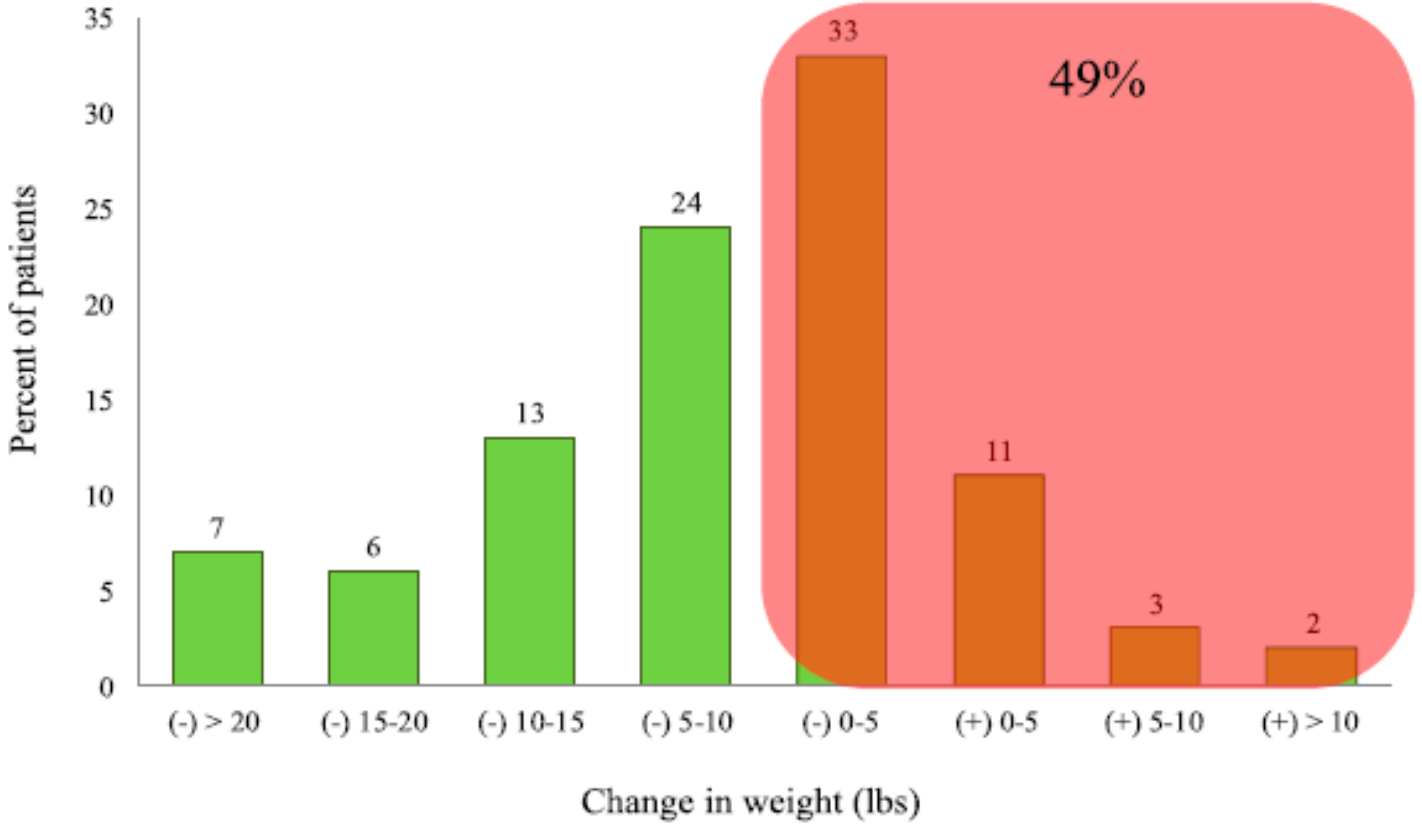


Figure 1. | Change in body weight at discharge based on Acute Decompensated Heart Failure National Registry database. Modified from reference 12, with permission.

Development of diuretic resistance is a well recognized challenge in the care of patients with ADHF and captures a subset of patients at high risk of morbidity and mortality.

Table 2. Proposed advantages and disadvantages of ultrafiltration

Advantages	Disadvantages
Reduction in renal venous congestion and improvement in renal hemodynamics	Lack of protective effect on renal function
Rapid and adjustable removal of fluid and improvement in symptoms of congestion	Lack of effect on markers of mortality (i.e., serum sodium level and BUN)
Higher mass clearance of sodium	Possible need for placement of midline or central venous catheter
Decreased risk of electrolyte abnormalities (e.g., hypokalemia)	Need for additional training for staff and physicians
Lack of neurohormonal activation (SNS, RAAS, and AVP)	Need for anticoagulation
Sustainability of the beneficial effects (e.g., effect on neurohormonal axis)	Complications related to extracorporeal circuit (e.g., allergic reaction, air embolism, hemolysis, infection, and bio-incompatibility)
Improvement in diuretic resistance, natriuresis, and urine output	Lack of widely accepted guidelines for its use (e.g., patient population, indications, timing of initiation and termination, and ultrafiltration rate/volume)
Decreased rate of heart failure–related rehospitalizations	Lack of knowledge on the long-term outcomes
Decreased hospital length of stay	High cost (device and disposables)
Availability of dedicated ultrafiltration devices that are portable, user-friendly, with minimal extracorporeal volume (33 ml), and have the ability of functioning with low blood flow rates (10–40 ml/min)	

SNS, sympathetic nervous system; RAAS, renin angiotensin aldosterone system; AVP, arginine vasopressin.

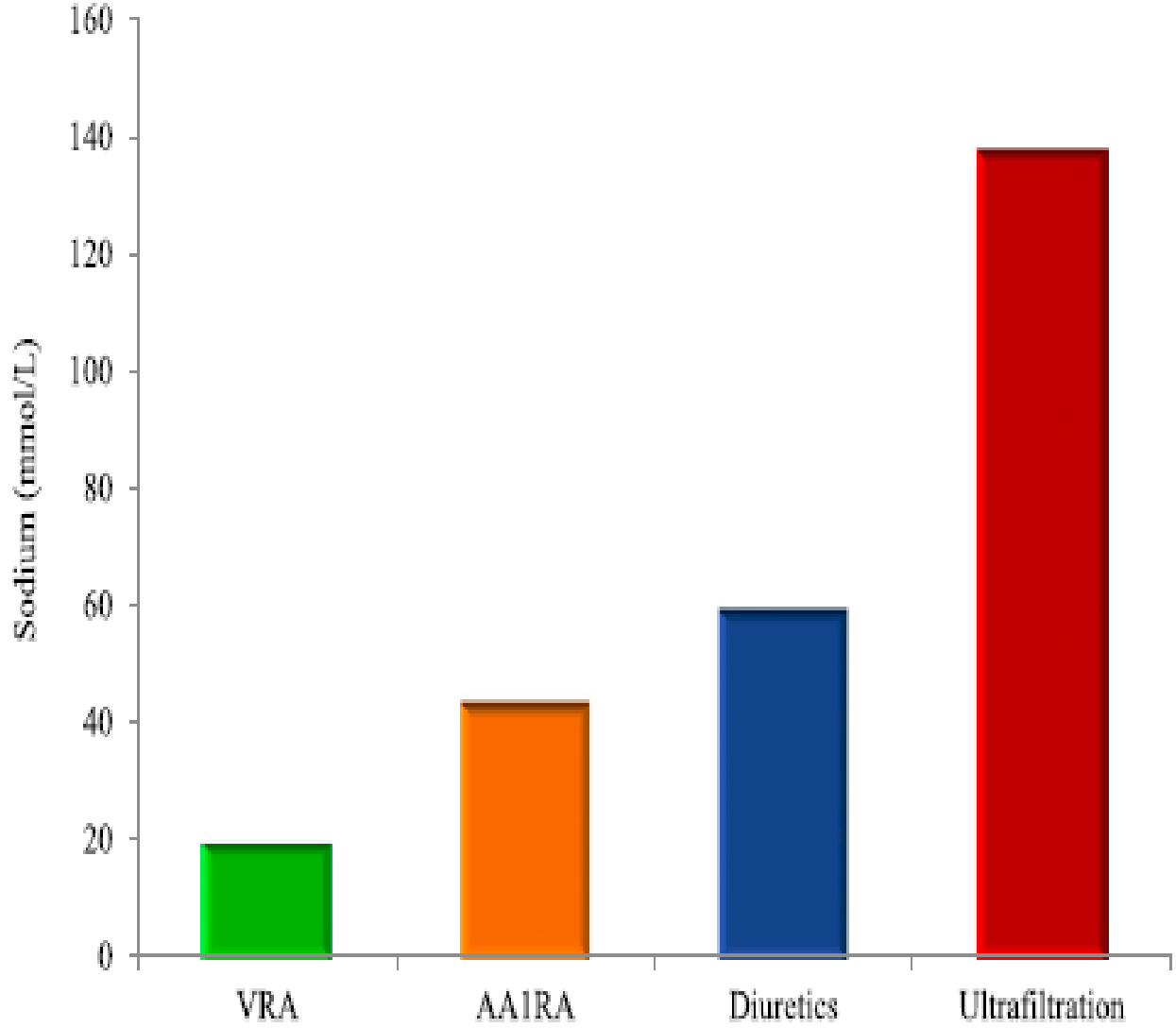


Figure 2. | Comparison of sodium removal with various treatment options. Whereas ultrafiltration extracts isotonic fluid from plasma, pharmacologic agents produce hypotonic urine containing lower concentrations of sodium. VRA, vasopressin receptor antagonists; AA1RA, adenosine-A1 receptor antagonists.

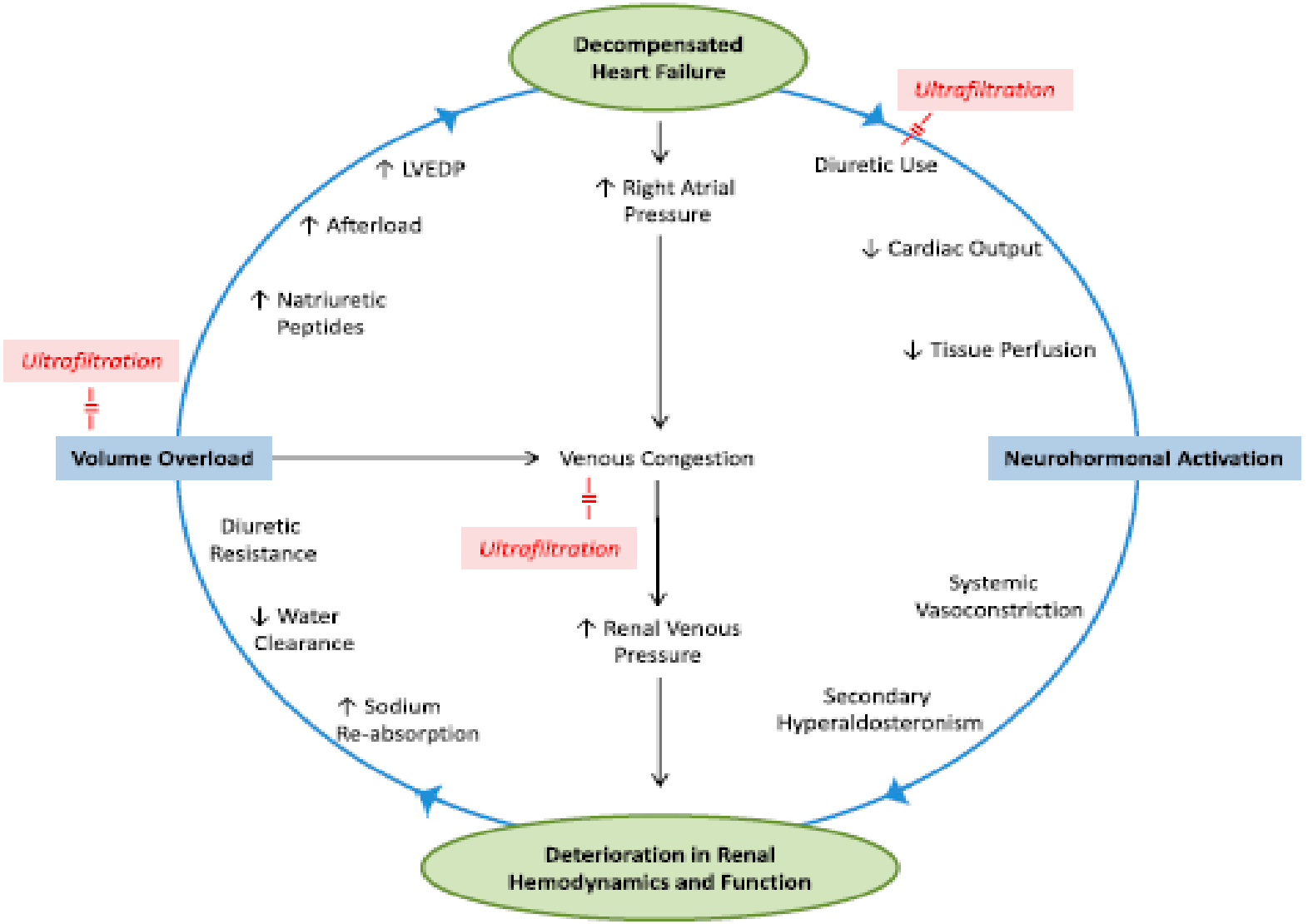


Figure 3. | **Proposed pathophysiologic pathways underlying decompensated heart failure and renal dysfunction.** Ultrafiltration could potentially counter certain interactions and break this vicious cycle via correction of fluid overload (while sparing the kidneys), venous decongestion, and increase in cardiac output (left shift of Frank Starling curve). In addition, diuretics can be held during ultrafiltration therapy potentially avoiding their downstream adverse effects (i.e., biologic holiday for cardiorenal interactions). LVEDP, left ventricular end diastolic pressure.

Table 5. Current guidelines on the use of ultrafiltration in heart failure

Reference	Guidelines
American College of Cardiology/American Heart Association (2009) (57)	Ultrafiltration is reasonable for patients with refractory congestion not responding to medical therapy; new recommendation If all diuretic strategies are unsuccessful, ultrafiltration or another renal replacement strategy may be reasonable Consultation with a kidney specialist may be appropriate before opting for any mechanical strategy to affect diuresis
Canadian Cardiovascular Society (2012) (58)	Venovenous ultrafiltration may be of benefit in relieving congestion particularly in diuretic-resistant patients Patients with persistent congestion despite diuretic therapy, with or without impaired renal function, may, under experienced supervision, receive continuous venovenous ultrafiltration
European Society of Cardiology (2012) (59)	Venovenous isolated ultrafiltration is sometimes used to remove fluid in patients with heart failure, although is usually reserved for those unresponsive or resistant to diuretics If doubling the dose of loop diuretics and infusion of dopamine do not result in an adequate diuresis and the patient remains in pulmonary edema, venovenous isolated ultrafiltration should be considered

UF Therapy for Heart Failure: The New Era

- The advent of portable devices with newer technology rendered UF more appealing and led to a second generation of clinical trials.
- These simplified and user-friendly machines have the advantages of small size, portability,

  blood flow rates of as low as 40 ml/min, and an extracorporeal blood volume of<50 ml.
- They can provide UF rate within a large spectrum (0–500 ml/h), do not mandate admission to intensive care unit, and have been marketed with the ability of even using peripheral veins.

Diuretics or Ultrafiltration for Acute Decompensated Heart Failure and Cardiorenal Syndrome?

- At the present time, we can recommend ultrafiltration only in patients with ADHF who are unable to achieve decongestion with a rational stepped-up diuretic regimen and usual hemodynamic care.

Bart BA, , et al. N Engl J Med. 2012.

Ultrafiltration in Decompensated Heart Failure with Cardiorenal Syndrome

Bradley A. Bart,etal, **N Engl J Med 2012;367:2296-304**

- **Background**
- Ultrafiltration is an alternative strategy to diuretic therapy for the treatment of patients with acute decompensated heart failure. Little is known about the efficacy and safety of ultrafiltration in patients with acute decompensated heart failure complicated by persistent congestion and worsened renal function. **Methods** We randomly assigned a total of 188 patients with acute decompensated heart failure,
- worsened renal function, and persistent congestion to a strategy of stepped pharmacologic therapy (94 patients) or ultrafiltration (94 patients). The primary end point was the bivariate change from baseline in the serum creatinine level and body weight, as assessed 96 hours after random assignment. Patients were followed for 60 days.
- **Results**
- Ultrafiltration was inferior to pharmacologic therapy with respect to the bivariate end point of the change in the serum creatinine level and body weight 96 hours after enrollment (P = 0.003), owing primarily to an increase in the creatinine level in the ultrafiltration group. At 96 hours, the mean change in the creatinine level was −0.04±0.53 mg per deciliter (−3.5±46.9 µmol per liter) in the pharmacologictherapy group, as compared with +0.23±0.70 mg per deciliter (20.3±61.9 µmol per liter) in the ultrafiltration group (P = 0.003). There was no significant difference in
- weight loss 96 hours after enrollment between patients in the pharmacologic-therapy group and those in the ultrafiltration group (a loss of 5.5±5.1 kg [12.1±11.3 lb] and 5.7±3.9 kg [12.6±8.5 lb], respectively; P = 0.58). A higher percentage of patients in the ultrafiltration group than in the pharmacologic-therapy group had a serious adverse event (72% vs. 57%, P = 0.03).
- **Conclusions**
- In a randomized trial involving patients hospitalized for acute decompensated heart failure, worsened renal function, and persistent congestion, the use of a stepped pharmacologic-therapy algorithm was superior to a strategy of ultrafiltration for the preservation of renal function at 96 hours, with a similar amount of weight loss with the two approaches. Ultrafiltration was associated with a higher rate of adverse events.

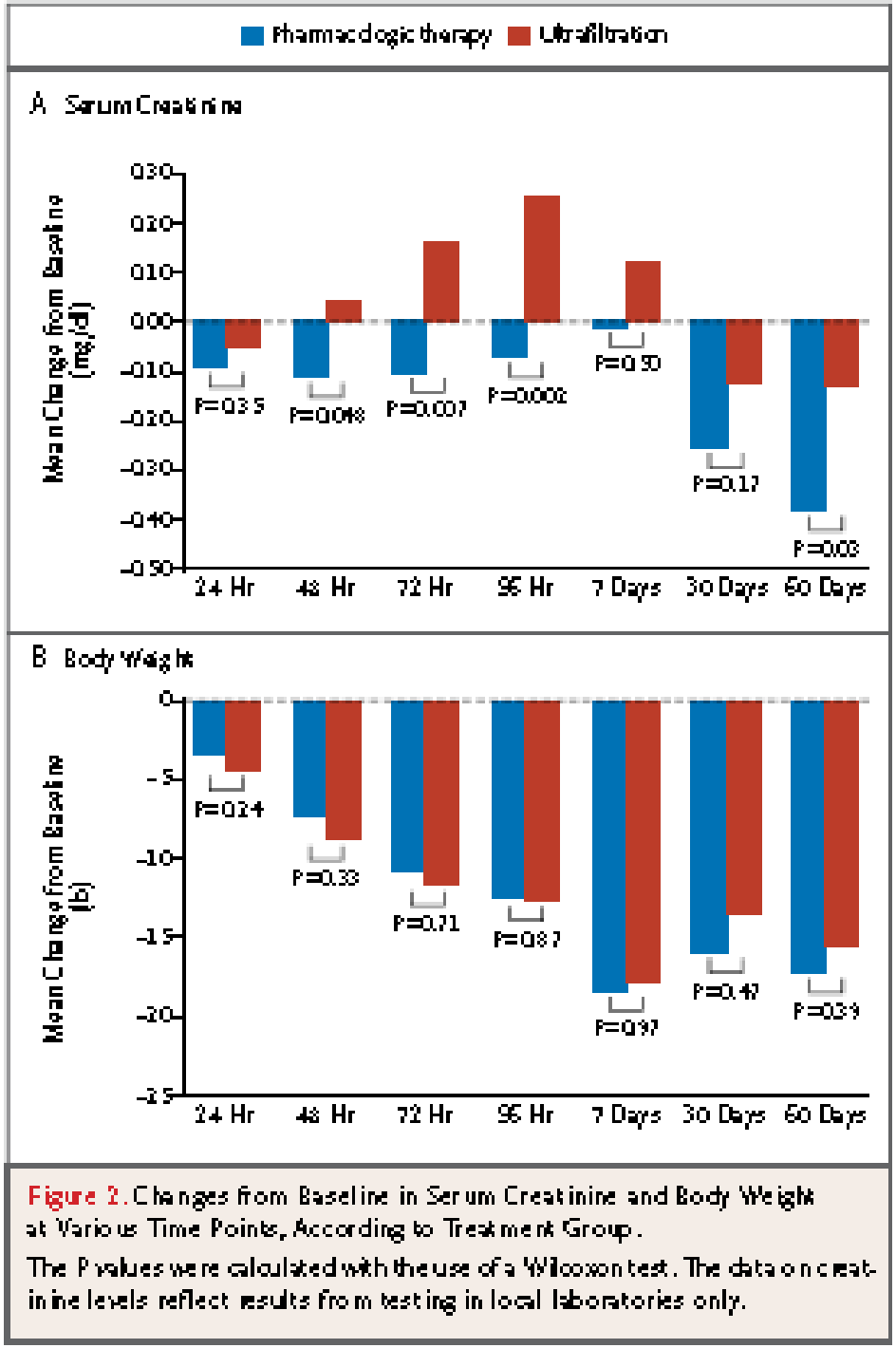


Figure 2. Changes from Baseline in Serum Creatinine and Body Weight at Various Time Points, According to Treatment Group.

The P values were calculated with the use of a Wilcoxon test. The data on creatinine levels reflect results from testing in local laboratories only.

Pharmacologic Alternatives

- A number of pharmacologic agents (e.g., endothelin receptor antagonists, vasopressin receptor antagonists, and adenosine-A1 receptor antagonists) have been used in trials in the hope of replacing or complementing conventional therapies but so far large-scale studies have unfortunately proven them to be suboptimal, ineffective, or unsafe (Kazory A, etalHeart Fail Rev 17: 1–16, 2012).


Thank You!